

REMARKSClaim Amendment

Claims 4-31, 34, 53, 54, 55 and 58 are cancelled.

Claim 1 has been amended to incorporate the subject matter of Claims 30 and 31. Claim 1 has further been amended to provide antecedent basis for the recitations of SEQ ID NOs: 1, 2, 3, and 4 in Claims 56 and 61.

Claims 32 and 33 have been amended to depend on Claim 1 in view of cancellation of Claim 30.

Claim 55 is cancelled in view of the amendment to Claim 1.

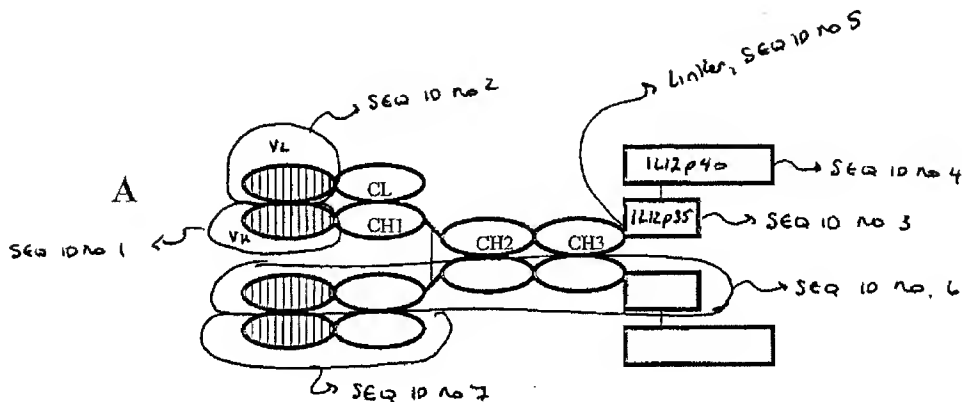
Claim 56 has been amended to recite that the compound comprises the polypeptide of SEQ ID NO: 6 and to delete the redundant recitations of the elements if SEQ ID NO: 6 (*i.e.* SEQ ID NOs: 1 and 3).

New Claim 59 is previously presented Claim 55 rewritten in an independent form.

New Claim 60 is based on now cancelled Claim 55 and is drawn to the subject matter now encompassed by Claim 1 as amended.

New Claim 61 is similar to Claim 56 as now amended, but recites that the compound comprises the polypeptide of SEQ ID NO: 7. As in Claim 56 as amended, the redundant recitations of the elements if SEQ ID NO: 7 (*i.e.* SEQ ID NO: 2) have been omitted.

To aid the Examiner in understanding the scope of the amended claim, Applicants reproduce an annotated version of FIG. 1 of the instant specification, as previously provided with the Amendment of February 18, 2010.



### Specification Amendment

Paragraphs [0037], [0038], [0039], [0165] and [0167] of the application as published (US2007/0202103) have been amended to correct an obvious typographical error by replacing the term “human” with the term “humanized.”

### Examiner's Interviews

The undersigned would like to thank Examiner David J. Blanchard for allowing the telephonic interviews on June 28, 2010 and July 8, 2010. During the interview of June 28, 2010, the Examiner discussed the status of Claims 30-33 with Susan M. Abelleira, Esq. The Interview Summary prepared by the Examiner for the interview of June 28, 2010, indicates that the proper status of Claims 30-33 is that these claims are objected to as being dependent upon a rejected base claim. However, during the interview of July 8, 2010 between the Examiner, Susan M. Abelleira, Esq. and the undersigned, the Examiner asserted that Claims 30-33 should now be considered rejected for the same reasons as 55-57. The remaining rejections of record, in particular, the non-obviousness of selecting the BC1 antibody for fusion with IL12, were also discussed during the interview of July 8, 2010.

### **I. Summary of the Office Action**

#### *(1) Objections to Specification*

Objections to the specification based on the description of BC1 antibody or its subunits as “human” are maintained.

#### *(2) Objection to Claims*

The Examiner objected to Claim 54 based on the recitation “humanized murine BC1 antibody.”

#### *(3) Rejection of Claim 15*

The rejection of Claim 15 as being indefinite under 35 U.S.C. §112, second paragraph, based on the recitation “FAB-like molecules” is maintained.

#### *(4) Rejection of Claims 5-6, 8-10 and 20*

The rejection of Claims 5-6, 8-10 and 20 as not enabled under 35 U.S.C. §112, first paragraph, is maintained. The Examiner's characterized the biological deposit made with

European Collection of Animal Cell Cultures under Accession No. 88042101, described in paragraph [0017] of the specification as published, as not meeting the test for “known and readily available.”

Rejections Based on Cited References: Points (5)-(8)

*(5) Rejection of Claims 1, 4-29, 34, 43-44 and new Claim 58*

The rejection of Claims 1, 4-39, 34, 43-44 as failing to comply with the written description under 35 U.S.C. §112, first paragraph, is maintained and is now applied to new Claim 58. This rejection is based on the Examiner's assertion that a genus of antibodies defined by its affinity to an antigen lack written description under 35 U.S.C. §112, first paragraph, where the antigen itself is not adequately described.

*(6) Rejection of Claims 1, 4-7, 11-27, 34, 43-44 and new Claims 53-54 and 57-58*

The rejection of Claims 1, 4-7, 11-27, 34, 43-44 as being unpatentable under 35 U.S.C. §103(a) is maintained and is now applied to new Claims 53-54 and 57-58. This rejection is based on the combination of references of Mariani I (Cancer, 80 (12 Suppl.):2484-2489, 1997) in view of Gillies [a] (The J. of Immunol., 160(12):6195-6203) and Gillies [b] (US 6,838,260). In view of the discussions during the interview of July 8, 2010, Applicants assume this rejection applies to Claims 30-33. If Applicants' assumption is incorrect, clarification is requested in the next communication from the Office.

*(7) Rejection of Claims 1, 5-6 and 8-10*

The rejection of Claims 1, 5-6 and 8-10 as being unpatentable under 35 U.S.C. §103(a) is maintained. This rejection is based on the combination of Mariani I, Gillies [a], Gillies [b] and of Scheier (J. Mol. Biol., 263:551-567, 1996).

*(8) Rejection of Claims 1, 26-29 and new Claims 55-56*

The rejection of Claims 1, 26-29 as being unpatentable under 35 U.S.C. §103(a) is maintained and is now applied to new Claims 55-56. This rejection is based on the combination of Mariani I, Gillies [a], Gillies [b] and Gillies [c] (WO 02/79232). In view of the discussions during the interview of July 8, 2010, Applicants assume this rejection applies to Claims 30-33. If Applicants' assumption is incorrect clarification is requested in the next communication from the Office.

(9) *Double Patenting Rejections*

The Examiner maintained the obviousness-type double-patenting rejections of Claims 1, 4-7, 11-27, 34, and 43-44 and also applied these rejections to new Claims 53-54 and 57-58:

- U.S. 7,226,998 in view of Mariani I and Gillies [a];
- U.S. 6,838,260 in view of Mariani I and Gillies [a]; and
- U.S. 6,617,135 in view of Mariani I and Gillies [a].

(10) *Response to Arguments*

In response to Applicants' argument that one of ordinary skill would not be motivated to select a BC1 antibody for further modification, and that the BC1-IL12 construct possesses unexpected advantages over IL12 alone or other IL12 antibody fusion proteins, the Examiner stated that Mariani I teaches that BC1 antibody showed favorable tumor targeting *in vivo* and that mere recognition of latent properties in the existing product does not render the claimed invention nonobvious.

## **II. Applicants' Response**

Applicants will address each of the above-numbered issues under the appropriate subheadings.

### **A. Objections Based on Informalities and Rejections Based on 35 U.S.C. §112**

(1) *Objections to Specification*

Applicants amended the specification to correct obvious typographical errors by replacing the term "human" with the term "humanized" where appropriate. Applicants again would like to clarify that the antibody known as BC1 is a murine antibody (*i.e.* an antibody produced by a murine hybridoma cell line), and that the "humanized" antibody is produced by grafting the complementarity-determining regions (CDRs) of BC1 onto a human IgG antibody. See, *e.g.*, paragraphs [0022-0023] of US2007/0202103.

Applicants believe that these amendments address the Examiner's objections.

(2) *Objection to Claims*

Applicants cancelled Claim 54, rendering the Examiner's objection moot.

(3) *Rejection of Claim 15*

Applicants cancelled Claim 15, rendering the Examiner's rejection moot.

*(4) Rejection of Claims 5-6, 8-10 and 20*

The Examiner characterized the biological deposit of the hybridoma cell producing BC1 monoclonal antibody made with European Collection of Animal Cell Cultures under Accession No. 88042101, described in paragraph [0017] of the specification as published, as not meeting the test for "known and readily available."

Applicants disagree with the Examiner's characterization of the biological deposit described in the present application. However, since Claims 5-6, 8-10 and 20 have been cancelled, the rejection of these claims is rendered moot. Furthermore, all of the remaining pending claims define the claimed subject matter in terms of disclosed or publically available sequences of biological polymers (proteins or nucleic acids). As such, the rationale for the rejection of Claims 5-6, 8-10 and 20 does not apply to the pending claims.

*(5) Rejection of Claims 1, 4-29, 34, 43-44 and new Claim 58*

The Examiner took the position that a genus of antibodies defined by its affinity to an antigen lack written description under 35 U.S.C. §112, first paragraph, where the antigen itself is not adequately described. It is Applicants' understanding that the Examiner's position is that the epitope to which the BC1 antibody shows affinity is not adequately described. If Applicants are incorrect, clarification is requested.

Applicants disagree with the Examiner's characterization of the instant specification. However, in the interest of expediting prosecution, Applicants have amended base Claim 1 and cancelled Claims 1, 4-29, 34, and 58.

*B. Rejections Based on Cited References (Points 5-8 Under Section I)*

The Examiner maintained previously advanced rejections (characterized above). The Examiner stated that Mariani I teaches monoclonal antibody BC1 that binds to human oncofetal fibronectin and shows favorable tumor targeting in vivo. The Examiner also stated, however, that Mariani I does not teach BC1-IL-12 fusion proteins, humanized BC1-IL-12 or scFv-IL-12 fusion proteins or wherein the BC1 comprises SEQ ID NO: 1 and SEQ ID NO: 2 or wherein IL-12 is human, wherein the IL-12p35 domain is conjugated to the IL-12p40 domain by a disulfide bond or a composition comprising the BC1-IL-12 fusion protein and a pharmaceutically

acceptable carrier. To cure the enumerated deficiencies, the Examiner is relying on Gillies [a] for its teaching of antibody-IL12 fusion protein comprising human p35 and p40 domains and on Gillies [b] for the additional teaching of a disulfide bond linking human p35 and p40 domains of IL-12. The Examiner stated that one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced BC1-IL12, humanized BC1-IL12 and like BC1-antigen binding fusion proteins including IL12. In addition, the Examiner is relying on Schier for its teaching of methods for producing a higher affinity antitumor antibody by restricting mutagenesis to the CDRs located at the center of the antibody combining site and on Gillies [c] for its teachings of modifying amino acid residues at the junction of an antibody-cytokine fusion protein to reduce immunogenicity. In response to Applicants' previous arguments, the Examiner stated that Mariani I teaches that BC1 antibody showed favorable tumor targeting in vivo and that mere recognition of latent properties in the existing product does not render the claimed invention obvious. Applicants will address the maintained rejections below based on the cited references and discussions between the undersigned and the Examiner during the interview of July 8, 2010.

Applicants submit that (1) one of ordinary skill in the art would *not* be motivated to select BC-1 monoclonal antibody for fusion with IL12, and that (2) use of the fusion protein defined by the pending claims as amended to target IL12 provides unexpected advantages over other fusion products used to target IL12. In support of their arguments, Applicants will rely on Exhibits B through F, described below.

Applicants previously provided Exhibit B, a copy of Chapter 14, "Recombinant Antibodies for Immunotherapy", by Nigel S. Courtenay-Luck and David Jones, Cambridge University Press (2009), and Exhibit C, a copy of K.-M. Lo et al. "HuBC1-IL12, an Immunocytokine Which Targets EDB-Containing Oncofetal Fibronectin in Tumors and Tumor Vasculature, Shows Potent Anti-Tumor Activity in Human Tumor Models", Cancer Immunol. Immunother. (2006). Applicants further provide herewith the following exhibits:

- Exhibit D, a copy of International Application publication WO 97/45544;
- Exhibit E, a copy of Castellani P. *et al.* "Differentiation Between High- and Low-Grade Astrocytoma Using a Human Recombinant Antibody to the Extra Domain-B of Fibronectin", American Journal of Pathology, Vol. 161, No. 5 (November 2002), pages 1695-1700; and

- Exhibit F, a copy of Midulla, M. *et al.* "Source of Oncofetal ED-B-containing Fibronectin: Implications of Production by Both Tumor and Endothelial Cells", Cancer Research (2000) Vol. 60, pp. 164-169.

(a) *At the Time the Present Invention Was Made one of Ordinary Skill in the art Would not be Motivated to Select BC1 Monoclonal Antibody for Targeting IL12*

The Examiner stated that Mariani I teaches monoclonal antibody BC1 that binds to human oncofetal fibronectin, extremely restricted in normal adult tissues, but highly expressed in tumors. The Examiner stated that Mariani I showed favorable tumor targeting *in vivo*.

In order to establish motivation for one of ordinary skill in the art to select BC1 for further modification required to arrive at the claimed invention, one would need to show (1) that BC1 selectively, or at least preferentially, binds to an epitope present only in malignant cells and (2) that even if one selected BC1, that success in arriving at a functional fusion product was expected. Neither one of these showings is made by Mariani I or any other reference of record.

The Examiner's attention is directed to Exhibit D, WO 97/45544. The priority date of WO 97/45544 is 24 May 1996, while the earliest presentation date for Mariani I is 3 June 1996. Referring to page 3, line 17 through page 4, line 35, Exhibit D describes that fibronectin, a glycoprotein present in both extracellular matrix and bodily fluids, is subject to alternative splicing. The fibronectin isoform containing "extra domain B," called ED-B fibronectin, is highly expressed in fetal and tumor tissues. Further, expression of "extra domain B" exposes a normally cryptic antigen within *another* domain of fibronectin ("type III repeat 7" domain). This cryptic epitope is thought to be the target of monoclonal antibody BC1. (*See esp.*, Exhibit D, page 4, lines 27-31.)

Exhibit D describes at page 4, line 36 through page 5, line 11 that, as of 1996, caveats remained to the specificity of BC1. Namely, it was not known whether the epitope recognized by BC1 is unmasked even when "extra domain B" is not expressed; thus, it was unknown in 1996 whether BC1 would cross-react with non-malignant tissues.

The doubts regarding the specificity of BC1 expressed in Exhibit D persisted in 2002. The Examiner's attention is directed to Exhibit E, Castellani *et al.* Referring to page 1699, left column, first paragraph, Exhibit E describes that it could not be *a priori* assumed that the epitope

recognized by BC1 would not become unmasked in the absence of “extra domain B.” Exhibit E suggests that an antibody that binds directly to “extra domain B” (rather than to the cryptic epitope within *another* domain of fibronectin) be used. Exhibit E reports the development of just such an antibody (a single chain Fv-type, scFv) named L19.

In combination, Exhibits D and E present evidence that prior to the claimed invention, there was doubt in the art regarding the target specificity and potential cross-reactivity of BC1. Furthermore, teachings existed at the time the present invention was made of a scFv L19 that targeted specifically “extra domain B,” restricted to malignant tissues, rather than an epitope that can also be present in normal tissues. Taken together, these teachings would direct one of ordinary skill *away* from selecting BC1 antibody.

There were further teachings in the art at the time of the present invention that suggest that if BC1 were selected, success in arriving at a functional product was not expected. The Examiner is again directed to Exhibit D, page 5, lines 29-33. Exhibit D describes that the cryptic epitope recognized by BC1 is likely absent from mouse fibronectin. To one of ordinary skill in the art this would indicate difficulties in working with animal models on which to test any BC1 fusion protein. Indeed, if murine tissues lack the BC1-cognate epitope, only expensive and complex human xenograft tumor models could be used for evaluation of any BC1 fusion protein efficacy.

The Examiner’s attention is further directed to Exhibit F, Midulla, *et al.* At page 168, the paragraph bridging the left and the right columns, Exhibit F describes that “attractiveness” of using BC1, an IgG antibody, is reduced by the authors’ discovery that ED-B fibronectin is *not* expressed in the lumen of blood vessels, resulting in the need for problematic penetration of vasculature by these large molecules. Exhibit F, similar to Exhibit E, suggests that using single chain Fv-type antibodies is preferable. Thus, the teachings of Exhibits E and F further direct one of ordinary skill in the art *away* from using BC1 antibody.

The arguments above, supported by Exhibits D through F, establish that one of ordinary skill in the art at the time when the claimed invention was made would not be motivated to select BC1 for targeting an effector molecule (IL12) to malignant cells. These arguments also establish that even if one were to select BC1 antibody for targeting an effector molecule (IL12) to the malignant cells, success would not be expected.



The teachings of Mariani I do nothing to dispel these doubts. Indeed, Mariani I did not control the reported data for binding of BC1 to fibronectin expressed in normal tissues. As such, Mariani I did not resolve the issues of possible cross-reactivity of BC1, and, consequently, did not establish that BC1, a large IgG antibody, would be effective for extravasation (in contravention of the teachings by Exhibit F). Thus, the teachings of Mariani I, even in combination with other references of record, are insufficient to establish obviousness of the claimed invention.

*(b) Against the Prevalent Teachings in the Contemporary Art, Applicants Employed BC1 Antibodies and Achieved Unexpected Advantages*

Despite the growing recognition in the art at the time the present invention was made that scFv antibodies, such as L19, are preferable for targeting effector molecules to fibronectin of malignant cells, Applicants employed an IgG-type BC1 antibody and discovered unexpected advantages. Applicants' argument, supported by Exhibits B and C, will be summarized below.

Exhibit C presents evidence that prevalent art expressed preference for scFv-type anti-ED-B antibody L19. Exhibit C, at page 456 (second to last page), left column, first full paragraph, states:

Although the observation that human B-FN was present in the vasculature of the human tumor implants in mice led to the conclusion that B-FN is produced by the tumor cells, this finding in itself does not preclude the possibility that murine B-FN is also produced by murine endothelial or accessory cells in the tumor vasculature. If this is indeed the case, targeting by huBC-1 in a xenograft model will not be as efficient and complete as L19, which recognizes the conserved ED-B domain and hence binds both human and murine B-FN. (*Emphasis added.*)

In other words, Exhibit C teaches *away* from the use of humanized BC1 and suggests using L19 instead.

Exhibit B presents further evidence of the difficulties faced by the researchers who contemplate using a BC-1 antibody for targeting. Exhibit B, page 193, second full paragraph states:

Although BC-1 was the first antibody to be raised to the ED-B antigen, it has been difficult to use in animal models for generating data that could support the clinical

use of this antigen as a target for immunotherapy. Although the ED-B sequence is conserved in many animals, and expressed in mice bearing human tumors, BC1 recognizes a cryptic epitope in the fibronectin molecule; this epitope is seen in human tissues, where this 91 amino acid domain is expressed and can be used in immunohistological studies, but it is not seen in human tumor xenograft models in mice. L19 recognizes a noncryptic epitope and has therefore been used in many in vivo studies to support the use of ED-B as a viable target for antibody therapy. (*Emphasis added.*)

Thus, Exhibit B teaches that BC-1 is difficult to work with, further suggesting that its development as a viable target for antibody therapy was considered inferior to L19.

However, the use of BC-1 antibody for targeting IL12 to malignant tissues produces unexpected advantages. For example, a first advantage is higher half-life of the BC-1, *i.e.* IgG-type antibody-IL-12 fusion protein, compared to L19, an scFv-IL-12 fusion protein. Exhibit C states on page 455, right column:

[...] the  $\beta$ -half life of 19 h for huBC1-mIL12 is significantly longer than that of another B-FN targeting fusion protein, mIL12-L19, comprising a single-chain murine IL12 fused with scFv (L19) ..., which does not have the benefit of the protective effect of the Fc-FcRn interaction ...

A second, and equally important advantage is that although BC1-IL12 fusion protein has lower activity than free IL12 (*see, e.g.,* the five plots at page 452 of Exhibit C), this very effect also reduces the toxicity of IL12. Because BC1-IL12 fusion protein possesses the effector function due to the presence of IgG moiety, such reduction in toxicity, even at the expense of activity, is advantageous. This is described on page 455, left column, of Exhibit C:

Overall, the BC1-IL12 fusion proteins have similar bioactivity as other Ab-IL12 fusion proteins, previously reported, and the reduced activity was likely a result of steric hindrance due to the large MW of this cytokine [11]. Given the highly toxic nature of IL12, this may be an advantage because lower activity would allow for the administration of a higher dosage. This may be clinically relevant because in addition to the potent immunostimulatory activities of IL12, the IgG1 isotype of the antibody fusion protein also has potent effector functions such as ADCC, which has been shown to play an important role in the mechanism of action for Rituxan and Herceptin [6]. While the activity of IL12 is dose-limiting, effector functions should increase with a higher dosage. (*Emphasis added.*)

Moreover, the Examiner's assertion that advantageous properties of BC1-IL12 fusion protein are the mere recognition of latent properties in the prior art is incorrect, because Applicants' claimed fusion proteins are not "an otherwise known invention" and would not be arrived at following the suggestion of the prior art. In fact, following the suggestion of the prior art, one of ordinary skill in the art would be deterred from using BC1. Finally, the low toxicity of BC1-IL12 fusion protein *is* stated to be surprising in Exhibit C, page 456, left column, first full paragraph:

Preliminary toxicity experiments in mice showed that the huBC1-muIL12 had surprisingly low toxicity in mice. (*Emphasis added.*)

The data presented in Exhibit C indicates that BC1-IL12 fusion protein possesses a higher therapeutic index than either IL12 alone or L19-IL12 fusion protein, as stated in Exhibit C, page 456, left column, second paragraph:

Given that the efficacious dose for huBC1-muIL12 is about 20 µg, this translates into a very favorable therapeutic index. We expect huBC1-huIL12, with a longer serum half-life, to show even better efficacy in the clinic, where patients during or post-chemotherapy still have a somewhat functional immune system that would benefit from multiple-cycles of treatment.

The evidence provided in Exhibits B and C supports the argument that Applicants use of BC1 IgG-type antibody for production of IL12 fusion protein went against the prevalent teachings in the art, and that the product defined by the pending claims showed unexpected combination of properties (low toxicity in combination with long half-life and the presence of the effector function), which renders the claimed fusion protein unexpected advantageous.

Reconsideration and withdrawal of the rejections are respectfully requested.

C. Double-Patenting Rejections (Point 9 Under Section I)

*U.S. 7,226,998 in View of Mariani I and Gillies [a]*

Claims 1, 4-7, 11-27, 34, and 43-44 and new Claims 53-54 and 57-58 are rejected on the grounds of non-statutory obviousness type double patenting as being unpatentable over Claims 1-8 of U.S. 7,226,998. In addition to the previously characterized of Mariani I and Gillies [a], the Examiner stated that Claims 1-8 of U.S. 7,226,998 are drawn to a fusion [protein] comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, which is

linked by a peptide bond to the p40 subunit of IL-12. The Examiner stated that although U.S. 7,226,998 does not expressly teach that the antibody be a BC1 antibody; however, Mariani I and Gillies [a] teach BC-1.

*U.S. 6,838,260 in View of Mariani I and Gillies [a]*

Claims 1, 4-7, 11-27, 34, and 43-44 and new Claims 53-54 and 57-58 are rejected on the grounds of non-statutory obviousness type double patenting as being unpatentable over Claims 1-3 and 6-8 of U.S. 6,838,260. In addition to the previously characterized references of Mariani I and Gillies [a], the Examiner stated that Claims 1-3 and 6-8 of U.S. 6,838,260 are drawn to a fusion protein comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, which is linked by a peptide bond to the p40 subunit of IL-12. The Examiner stated that although Claims 1-3 and 6-8 of U.S. 6,838,260 do not expressly teach that the antibody be a BC-1 antibody; however, Mariani I and Gillies [a] teach BC-1.

*U.S. 6,617,135 in View of Mariani and Gillies [a]*

Claims 1, 4-7, 11-27, 34, and 43-44 and new Claims 53-54 and 57-58 are rejected on the grounds of non-statutory obviousness type double patenting as being unpatentable over Claims 1-3, 7 and 10 of U.S. 6,617,135. In addition to the previously characterized references of Mariani I and Gillies [a], the Examiner stated that Claims 1-3, 7 and 10 of U.S. 6,617,135 are drawn to a fusion protein comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, which is linked by a peptide bond to the p40 subunit of IL-12. The Examiner stated that although Claims 1-3 and 6-8 of U.S. 6,838,260 do not expressly teach that the antibody be a BC-1 antibody; however, Mariani I and Gillies [a] teach BC-1.

Applicants note that a double patenting rejection of the obviousness-type is analogous to a rejection based on a failure to meet the requirements of 35 U.S.C. §103(a). Accordingly, as stated in MPEP §804(II)(B)(1), the analysis employed in an obviousness-type double patenting determination parallels the guidelines for 35 U.S.C. §103(a) rejection. Therefore, in response to the double-patenting rejections, Applicants recapitulate their arguments presented above, in the section II.C, titled "Rejections Based on Cited References (Points 5-8 Under Section I)." The claims of U.S. 7,226,998, U.S. 6,838,260 and U.S. 6,617,135 go no further than other references cited by the Examiner and discussed above. Applicants submit that nothing in the cited claims of the U.S. 7,226,998, U.S. 6,838,260 or U.S. 6,617,135 (1) motivates one of

ordinary skill in the art to select BC-1 monoclonal antibodies for fusion with IL12, and that (2) suggests that the use of the fusion protein defined by the pending claims as amended to target IL12 would provide unexpected advantages over other fusion products used to target IL12. Therefore, the present invention is non-obvious.

Reconsideration and withdrawal of the rejections are respectfully requested.

**Information Disclosure Statement**

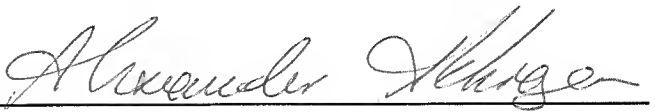
An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

**CONCLUSION**

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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